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Quetiapine dose for people with schizophrenia (Protocol)

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[Intervention Protocol]

Quetiapine dose for people with schizophrenia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of quetiapine dosage for people with schizophrenia and schizophrenia-related disorders.

BACKGROUND

Description of the condition

Schizophrenia is a severe and enduring mental illness characterised by distortions in perception and cognition. Symptoms of schizophrenia can be categorised into two main groups of positive and negative symptoms (WHO 1994; APA 2013). Positive symptoms signify changes in thought or behaviour, or both, which include fixed, false beliefs (delusions), perceptions without cause (hallucinations), thought insertion or withdrawal, thought broadcasting, bizarre posturing and behaviours such as catatonia (Carpenter 1994; Blows 2010). Negative symptoms represent apathy or lack of motivation (avolition), lack of pleasure (anhedonia), blunting of affect, declining in social functioning, disorganisation of behaviour and thought (Carpenter 1994; Blows 2010; Kuipers 2014). For a person to be diagnosed with schizophrenia they must exhibit at least both positive and negative symptoms for six months, with at least one symptom active during the prior month (APA 2013). More recently, International Classification of Diseases 11th Revision (ICD-11) has updated the schizophrenia definition; however the core symptoms remain similar (WHO 2018).

The course of schizophrenia is unpredictable and varies from partial to full remission, continuous or episodic with progressive or stable deficits (ICD-10) (WHO 1994). Only one in six people who experience a psychotic episode recover fully and approximately 50% of people with a severe mental illness, such as schizophrenia, are treatment-resistant (Marwaha 2004). The effect of schizophrenia can precipitate an increased risk of suicide (Tsuang 1978; Hor 2010), with an estimated suicide rate of 10% (Palmer 2005; Hor 2010). People who live with this chronic illness also experience frequent hospitalisation, deprivation of liberty, high rates of relapse, financial problems, legal difficulties, stigma, isolation and comorbid medical conditions (Pankey 2003; Harrison 2010). People with schizophrenia are more likely to be single and around

80% to 90% are unemployed (Marwaha 2004; Messias 2007).
The World Health Organization (WHO) estimates that schizophrenia affects more than 23 million people worldwide and commonly starts earlier in males (WHO 2003; WHO Factsheet 2018). Schizophrenia affects about 7 in 1000 adults, with first episode onset typically occurring between the ages of 15 to 35 years (Kuipers 2014). The point prevalence averages approximately 4.5 per population of 1000, and the risk of developing the illness over one's lifetime averages 0.7% (Tandon 2008). A recent systematic review estimated schizophrenia costs the global economy between USD 94 million to USD 102 billion per annum (Chong 2014). Schizophrenia is associated with considerable disability and may affect educational and occupational performance (WHO Factsheet 2018). People with schizophrenia have a mortality rate two to three times that of the general population; with men dying 20 years and women 15 years earlier than those who do not have schizophrenia (Saha 2007; Brown 2010; Kuipers 2014).

Description of the intervention

The mainstay treatment for schizophrenia is antipsychotic medication. Quetiapine is an antipsychotic used in the treatment of schizophrenia, bipolar affective disorder and major depression. It has been shown to be effective in the treatment of people with schizophrenia with similar efficacy to other antipsychotics (Srisurrapanont 2004); the only exception is clozapine which has superiority over other antipsychotics (Kane 1988; Essali 2009).
After administration, quetiapine is rapidly absorbed with a peak plasma concentration reached around 1 to 1.8 hours with a half-life (T½) of around 7 hours (Markowitz 1999). Steady-state peak concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. Bioavailability is not significantly affected by the administration of food (DeVane 2001). Quetiapine is approximately 83% bound to plasma proteins. Its main route of metabolism is predominantly by the hepatic enzyme CYP3A4 with minor metabolism through CYP2D6; its mean elimination half-life is approximately 6 hours (DeVane 2001), with less than 5% of the drug excreted unchanged (Markowitz 1999).
The most common side effects associated with quetiapine are sedation, dizziness, headache, dry mouth, metabolic side effects (changes in blood lipids and weight gain), constipation and dizziness; other side effects include extrapyramidal side effects (stiffness, tremors, abnormal movements and restlessness), decreases in blood haemoglobin levels, increased heart rate, blurred vision and peripheral oedema (Calabrese 2005; EMC 2018).
For the treatment of schizophrenia, quetiapine is usually administered twice a day orally. The usual effective dose range is 300 mg/day to 450 mg/day. However, depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 mg/day to 750 mg/day (BNF 2018; EMC 2018).

How the intervention might work

Quetiapine, an atypical dibenzothiazepine antipsychotic has antagonist properties at 5 hydroxytryptamine 2A (5HT2A) receptors and dopaminergic D2 receptors with a higher affinity for 5-HT2A than for D2 receptors (Tasman 2008). The stronger 5HT2A antagonism increases dopaminergic neurotransmission in the nigrostriatal pathways, hence leading to less extrapyramidal side effects and theoretically improving negative symptoms in schizophrenia by increasing the release of dopamine or acetylcholine, or both, in the prefrontal cortex (Miyamoto 2012). It is a partial agonist at 5-HT1A receptors. The blockade of 5-HT2 receptors and the induction of brain-derived neurotrophic factor (BDNF) are the pivotal characters of atypical antipsychotic medications and the stimulation of 5-HT1A receptors sometimes contributes to 'atypicality' (Kusum 2015). It is also antagonist at histamine H1 and adrenergic alpha 1 receptors.
Quetiapine might exert its antipsychotic effects by the "kiss and run" mechanism proposed by Kapur 2000, where quetiapine has a rapid dissociation from D2 receptors (Kapur 2000; Kapur 2001; Schatzberg 2009). A review by Seeman 2002 shows that quetiapine and other newer, second generation, antipsychotic drugs help clinically by binding more loosely than dopamine to the D2 receptors and dissociate rapidly to allow normal dopamine neurotransmission.
Studies have also demonstrated protective effects of quetiapine and other atypical antipsychotic drugs on apoptosis with neuronal cell culture (Gil-ad 2001; Qing 2003). This points towards a potentially different mechanism of action of atypical antipsychotic drugs.
In people with acute schizophrenia, Small 1997 found a positive correlation between the dose of quetiapine and reduction in Brief Psychiatric Rating Scale (BPRS; an instrument to assess symptoms of psychosis) scores in comparison with placebo, as did Arvanitis 1997 across four fixed doses of immediate release quetiapine (150 mg, 300 mg, 600 mg, or 750 mg daily) with no significant differences in extrapyramidal side effects. Buckley 2004's analysis of three double-blinded randomised controlled trials (RCTs) found that quetiapine is effective across both domains of positive and negative symptoms of schizophrenia, including depression and agitation. Srisurrapanont 2004 established that quetiapine showed slight improvement on positive and negative symptoms, as measured by mental states using BPRS and Positive and Negative Syndrome Scale (PANSS). Srisurrapanont 2004 posited there are little to no data on the effects of quetiapine on social functioning and quality of life.

Why it is important to do this review

Most people diagnosed with schizophrenia require both antipsychotic treatment and additional psychosocial support with continued follow-up. The cost of continued care is expensive but rela-

tively small compared to the advantages of enhanced quality of life and functionality (WHO 2003). Undertaking risk-benefit analyses and finding effective evidence-based treatments is vital.

Quetiapine is an effective antipsychotic for people with schizophrenia (Srisurrapanont 2004), but uncertainties prevail about quetiapine dosage. Results from a meta-analysis concerning high-dose (750 mg/day to 800 mg/day) versus low-dose (300 mg/day to 400 mg/day) quetiapine in terms of the response rate, changes in positive symptoms and discontinuation rate (due to either adverse effects or no response) showed no statistically significant difference amid both categories of treatment (high- and low-dose quetiapine) (Citrome 2005; Painuly 2010). Sparshatt 2008 and Buckley 2004 found similar results. On the other hand, Kahn 2007, found a statistically significant correlation between increasing the dose and a positive therapeutic effect.

The choice of the dose of quetiapine is guided by the risk-benefit analysis. Common side effects of quetiapine include sedation, dizziness, asthenia (lack of energy) and dry mouth but, in comparison with other antipsychotics such as haloperidol and chlorpromazine, quetiapine has lower association with extra-pyramidal side effects (Srisurrapanont 2004). Dose-related side effects, especially the risk of cardiac-sudden death (Ray 2009), remains a limiting factor in abiding by guidelines that supports high dose for an enhanced response. Dose of quetiapine in clinical practice is influenced by factors, such as length of stay in hospital and prior hospitalisation. However, there is no clear evidence to guide the practice of using high dosage in such cases (Citrome 2005).

According to Srisurrapanont 2004, the usual clinical practice has not been explored in depth. It is important to clarify what dose of quetiapine should be prescribed under what circumstances and at which particular phase of illness. For instance, in acute phase, the quetiapine dose range used is higher than that in the maintenance phase as with other antipsychotic drugs; however, this range differs between studies (McCue 2006; McEvoy 2006; Riedel 2007; Sparshatt 2008).

This Cochrane Review aims to provide clarity about the effects of quetiapine dose range for people with schizophrenia, including different preparations, by assessing evidence available from RCTs.

OBJECTIVES

To assess the effects of quetiapine dosage for people with schizophrenia and schizophrenia-related disorders.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs that meet the inclusion criteria and report useable data. We will exclude quasi-randomised studies, such as those that allocate intervention by alternate days of the week. Where people are given additional treatments as well as quetiapine, we will only include data if the adjunct treatment is evenly distributed between groups and only treatment with quetiapine is randomised.

Types of participants

Adults (aged 16 years and older) with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder (diagnosed using a standardised criteria (e.g.International Classification of Diseases (ICD), Diagnositc and Statistical Manual of Mental Disorders (DSM) or by a psychiatrist). We will also include trials in which participants have a range of diagnoses, provided most participants (over 50%) have a diagnosis of schizophrenia or related disorder.

We wish to ensure the information is as relevant as possible to the current care of people with schizophrenia. We aim to highlight the current clinical state clearly (acute, early post-acute, partial remission, remission), the stage (prodromal, first episode, early illness, persistent), and whether the studies primarily focused on people with particular problems (e.g. negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Quetiapine dose: oral immediate release, oral modified release

1.1 Low: less than 300 mg daily
1.2 Medium: 300 mg to 600 mg (usual dose) daily
1.3 High: more than 600 mg daily (for both immediate release and modified release preparations)

2. Placebo

3. Other antipsychotic medication: any dose

Types of outcome measures

We aim to divide all outcomes into short-term (less than 6 weeks), medium-term (6 weeks to 6 months) and long-term (more than 6 months).

We will endeavour to report binary outcomes recording clear and clinically meaningful degrees of change (e.g. global impression of much improved, or more than 50% improvement on a valid rating

scale - as defined within the trials) before any others. Thereafter we will list other binary outcomes and then those that are continuous. For outcomes such as 'clinically important change', 'any change', and 'relapse', we will use the definition used by the trial authors. For valid scales please see the Data extraction and management section.

Primary outcomes

1. Global state

1.1 Clinically important change in global state

2. Quality of life

2.1 Clinically important change in quality of life

3. Adverse effect

3.1 Specific: sedation

Secondary outcomes

1. Global state

1.1 Any change in global state
1.2 Average endpoint or change score on a global state scale

2. Quality of life

2.1 Any change in quality of life
2.2 Average endpoint score on quality of life scale

3. Adverse effects

3.1 General

3.1.1 At least one clinically important adverse effect/event
3.1.2 Average endpoint or change score on adverse effect scale

3.2 Specific effects

3.2.1 Extrapyramidal side effects
3.2.2 Metabolic effects
3.2.3 Cardiovascular effects
3.2.4 Various other effects
3.3 Death: suicide or any cause.

4. Mental state

4.1 General

4.1.1 Clinically important change in general mental state
4.1.2 Any change in general mental state
4.1.3 Average endpoint or change score on a general mental state scale

4.2 Specific symptoms (e.g. positive, negative, affective)

4.2.1 Clinically important change in specific symptoms
4.2.2 Any change in specific symptoms
4.2.3 Average endpoint or change score on a specific symptoms scale

5. Functioning

5.1 General

5.1.1 Clinically important change in general functioning
5.1.2 Any change in general functioning
5.1.3 Average endpoint or change score on general functioning scale

5.2 Social or life skills

5.2.1 Clinically important change in social functioning or life skills
5.2.2 Any change in social functioning or life skills
5.2.3 Average endpoint or change score on social functioning or life skills scale

6. Leaving the study early

6.1 For any reason
6.2 For specific reason

7. Service use

7.1 Hospital admission
7.2 Time in hospital

'Summary of findings' table

We will use the GRADE approach to interpret findings (Schünemann 2011). To create a 'Summary of findings' table we will use GRADEpro GDT 2015 to export data from the Review Manager file (Review Manager 2014). These tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rate as important to patient care and decision making. We aim to select the following clinically important outcomes for inclusion in the 'Summary of findings' table:

1. Global state: clinically important change in global state
2. Quality of life: clinically important change in quality of life
3. Adverse effects: sedation
4. Mental state: clinically important change in general mental state
5. Leaving the study early: for any reason
6. Leaving the study early: for specific reason
7. Service use: hospital admission

If data are unavailable for these pre-specified outcomes but are available for ones that are similar, we will present the closest outcome to the pre-specified one in the table. However, we will take this into account when assessing the certainty of the evidence for the finding.

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

The Information Specialist of the Cochrane Schizophrenia Group will search the register using the following search strategy:
(*Quetiapine* AND *Dosage*) in Intervention Field of STUDY
In this study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Shokraneh 2017; Shokraneh 2018).
This register is compiled by systematic searches of major resources (AMED, BIOSIS, CENTRAL, CINAHL, ClinicalTrials.gov, Embase, MEDLINE, PsycINFO, PubMed, the World Health Organization International Clinical Trial Registry Platform (WHO ICTRP)) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, handsearches, grey literature and conference proceedings (see the Cochrane Schizophrenia Group's website for further information: http://schizophrenia.cochrane.org/register-trials). There are no language, date, document type or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We will inspect references of all included studies for further relevant studies.

2. Personal contact

We will contact the first author of each included study for information regarding unpublished trials. We will note the outcome of this contact in the 'Included studies' or 'Studies awaiting classification' tables.

Data collection and analysis

Selection of studies

For this Cochrane Review, review authors CC and YI will examine the search results by title, and will obtain all potentially relevant abstracts for assessment. We will classify the articles as either included, excluded or 'with information missing'. Review author MW will independently re-inspect a random 20% sample to ensure reliability. Where disputes arise, we will acquire the full-text report for more detailed scrutiny. Review authors CC and YI will obtain and independently inspect the full-text articles that potentially meet the inclusion criteria. Review author MW will inspect a random 20% of these full-text reports in order to ensure reliable selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the study authors for clarification. We will list studies excluded after full-text assessment and the reasons for exclusion in a 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

1. Extraction

Review authors YI, CC and HE will extract data from all included studies. In addition, to ensure reliability, and review author MW will independently extract data from a random sample of these studies, comprising 10% of the total. We will attempt to extract data presented only in graphs and figures whenever possible, but will include only if two review authors independently obtain the

same result. If studies are multicentre, where possible we will extract data relevant to each. We will discuss any disagreement and document our decisions. If necessary, we will attempt to contact study authors through an open-ended request in order to obtain missing information or for clarification. Review authors YI and HE will help clarify issues regarding any remaining problems and we will document these final decisions.

2. Management

2.1 Forms

We will extract data onto standard, pre-designed data extraction forms.

2.2 Scale-derived data

We will include continuous data from rating scales only if:

1. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000);
2. the measuring instrument has not been written or modified by one of the trial authors for that particular trial; and
3. the instrument should be a global assessment of an area of functioning and not subscores which are not, in themselves, validated or shown to be reliable. However there are exceptions, we will include subscores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in 'Description of studies' we will note if this is the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data: change data can remove a component of between-person variability from the analysis; however, calculation of change needs two assessments (baseline and endpoint) that can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We have decided primarily to use endpoint data, and only use change data if the former are not available. If necessary, we will combine endpoint and change data in the analysis, as we prefer to use mean differences (MDs) rather than standardised mean differences (SMDs) throughout (Deeks 2011).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we will apply the following standards to relevant continuous data before inclusion.

For endpoint data from studies including fewer than 200 participants:

1. when a scale starts from the nite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation (SD). If this value is lower than one, it strongly suggests that the data are skewed and we will exclude these data. If this ratio is higher than one but less than two, there is suggestion that the data are skewed: we will enter these data and test whether their inclusion or exclusion would change the results substantially. If such data change results we will enter as 'other data'. Finally, if the ratio is larger than two we will include these data, because it is less likely that they are skewed (Altman 1996).
2. if a scale starts from a positive value (such as the PANSS, which can have values from 30 to 210 (Kay 1986)), we will modify the calculation described above to take the scale starting point into account. In these cases skewed data are present if 2 SD > (S − S min), where S is the mean score and 'S min' is the minimum score.

Please note that we will enter all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We will also enter all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether or not data are skewed.

2.5 Common measurement

To facilitate comparison between trials we aim, where relevant, to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we will make efforts to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the BPRS (Overall 1962), or the PANSS (Kay 1986), this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds are not available, we will use the primary cut-off presented by the study authors.

2.7 Direction of graphs

Where possible, we will enter data in such a way that the area to the left of the line of no effect indicates a favourable outcome for high dosage quetiapine. Where keeping to this makes it impossible to

avoid outcome titles with clumsy double-negatives (e.g. 'not unimproved') we will report data where the left of the line indicates an unfavourable outcome and note this in the relevant graphs.

Assessment of risk of bias in included studies

Review authors YI, CC, MW and HE will independently assess risk of bias using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011a). This set of criteria is based on evidence of associations between potential overestimation of effect and the level of risk of bias of the article that may be due to aspects of sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting, or the way in which these 'domains' are reported.

If the review authors disagree, we will make the final rating by consensus. Where inadequate details of randomisation and other characteristics of trials are provided, we will attempt to contact study authors to obtain further information. We will report non-concurrence in quality assessment, but if disputes arise regarding the category to which a trial is to be allocated, we will resolve this by discussion.

We will note the level of risk of bias in the review text, Risk of bias tables, and the 'Summary of findings' table(s).

Measures of treatment effect

1. Binary data

For binary outcomes we will calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI), as it has been shown that RR is more intuitive than odds ratios (OR) (Boissel 1999); and that OR tend to be interpreted as RR by clinicians (Deeks 2000). Although the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), with their CIs, are intuitively attractive to clinicians, they are problematic to calculate and interpret in meta-analyses (Hutton 2009). For binary data presented in the 'Summary of findings' table(s) we will, where possible, calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes we will estimate MD between groups. We prefer not to calculate effect size measures (SMD). However if trials use scales of very considerable similarity, we will presume there is a small difference in measurement, and we will calculate effect size and transform the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Study authors often fail to account for intra-class correlation in clustered studies, leading to a unit-of-analysis error whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but adjust for the clustering effect.

Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will seek to contact the first authors of studies to obtain intra-class correlation coefficient (ICC) values for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

We have sought statistical advice and have been advised that the binary data from cluster trials presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC: thus design effect = 1 + (m − 1) * ICC (Donner 2002). If the ICC is not reported we will assume it to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed and taken ICCs and relevant data documented in the report into account, synthesis with other studies will be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, participants can differ significantly from their initial state at entry to the second phase, despite a washout phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both carry-over and unstable conditions are very likely in severe mental illness, we will only use data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. If data are binary, we will add these and combine within the two-by-two table. If data are continuous, we will combine data following the formula provided in the *Cochrane Handbook for Systematic*

Reviews of Interventions (Higgins 2011b). Where additional treatment arms are irrelevant to this review, we will not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We choose that, for any particular outcome, should more than 50% of data be unaccounted for we will not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study are lost, but the total loss is less than 50%, we will address this within the 'Summary of findings' table(s) by downgrading the certainty of the evidence. Finally, we will also downgrade the certainty of the evidence within the 'Summary of findings' table(s) should the loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0% and 50% and where these data are not clearly described, we will present data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed. We will use the rate of those who stay in the study - in that particular arm of the trial - and apply this also to those who did not. We will undertake a sensitivity analysis testing how prone the primary outcomes are to change when data only from people who complete the study to that point are compared to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

We will use data where attrition for a continuous outcome is between 0% and 50%, and data only from participants who complete the study to that point are reported.

3.2 Standard deviations

If SDs are not reported, we will try to obtain the missing values from the study authors. If these are not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we can calculate SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). When only the SE is reported, SDs are calculated by the formula SD = SE * $\sqrt{}$(n). The *Cochrane Handbook for Systematic Reviews of Interventions* presents detailed formulae for estimating SDs from P, t or F values, CIs, ranges or other statistics (Higgins 2011b). If these formulae do not apply, we will calculate the SDs according to a validated imputation method, which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. Nevertheless, we will examine the validity of the imputations in a sensitivity analysis that excludes imputed values.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers; others use the method of last observation carried forward (LOCF); while more recently, methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences between groups in their reasons for doing so is often the core problem in randomised schizophrenia trials. We will therefore not exclude studies based on the statistical approach used. However, by preference we will use the more sophisticated approaches, i.e. we will prefer to use MMRM or multiple-imputation to LOCF, and we will only present completer analyses if some kind of ITT data are not available at all. Moreover, we will address this issue in the item 'Incomplete outcome data' of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will simply inspect all studies for participants who are clearly outliers or situations that we had not predicted would arise and, where found, discuss such situations or participant groups.

2. Methodological heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We will simply inspect all studies for clearly outlying methods which we had not predicted would arise and discuss any such methodological outliers.

3. Statistical heterogeneity

3.1 Visual inspection

We will inspect graphs visually to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We will investigate heterogeneity between studies by considering the I^2 statistic alongside the Chi^2 P value. The I^2 statistic provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 statistic depends on the magnitude and direction of effects as well as the strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2 statistic). We will interpret an I^2 estimate greater than or equal to 50% and accompanied by a statistically significant Chi^2 statistic as evidence of substantial heterogeneity (Deeks 2011). When substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for heterogeneity (see the Subgroup analysis and investigation of heterogeneity section).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10.1 of the *Cochrane Handbook for Systemic reviews of Interventions* (Sterne 2011).

1. Protocol versus full study

We will try to locate protocols of included randomised trials. If the protocol is available, we will compare outcomes in the protocol and in the published report . If the protocol is not available, we will compare outcomes listed in the methods section of the trial report with actually reported results.

2. Funnel plot

We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We will not use funnel plots for outcomes where there are ten or fewer studies, or where all studies are of similar size. In other cases, where funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies, even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model: it puts added weight onto small studies, which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. With this in mind, we will use a fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We do not anticipate performing subgroup analysis, considering limited available evidence of quetiapine dosage in schizophrenia. If data are available we will, for primary outcomes, perform a subgroup analysis to test if dose of quetiapine has different effects for adolescents (16 to 18 years) compared with adults (over 18 years).

2. Investigation of heterogeneity

We will report if inconsistency is high. Firstly, we will investigate whether data have been entered correctly. Secondly, if data are correct, we will inspect the graph visually and remove outlying studies successively to see if homogeneity is restored. For this review we have decided that should this occur with data contributing to the summary finding of no more than 10% of the total weighting, we will present data. If not, we will not pool these data and will discuss any issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity is obvious, we will simply state hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

If there are substantial differences in the direction or precision of effect estimates in the sensitivity analyses listed below, we will not add data from the lower-quality studies to the results of the higher-quality trials, but will present these data within a subcategory. If their inclusion does not result in a substantive difference, they will remain in the analyses.

1. Implication of randomisation

If trials are described in some way as to imply randomisation, for the primary outcomes, we will pool data from the implied trials with trials that are randomised.

2. Assumptions for lost binary data

Where assumptions have to be made regarding people lost to follow-up (see Dealing with missing data) we will compare the findings of the primary outcomes when we use our assumption compared with completer data only. If there is a substantial difference, we will report results and discuss them but continue to employ our assumption.

Where assumptions have to be made regarding missing SDs (see Dealing with missing data), we will compare the findings on primary outcomes when we use our assumption compared with completer data only. We will undertake a sensitivity analysis testing how prone results are to change when 'completer' data only are compared to the imputed data using the above assumption. If there is a substantial difference, we will report results and discuss them but continue to employ our assumption.

3. Risk of bias

We will analyse the effects of excluding trials that are at high risk of bias across one or more of the domains (see Assessment of risk of bias in included studies) for the meta-analysis of the primary outcome.

4. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we use imputed values for ICC in calculating the design effect in cluster-randomised trials.

5. Fixed- and random-effects

We will synthesise data using a fixed-effect model taking into the account the relative advantages and disadvantages of a fixed-effect versus random-effect. However, we will also synthesise data for the primary outcome using the random-effects model to evaluate whether this alters the significance of the results.

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The Cochrane Schizophrenia Group Editorial Base at The University of Nottingham, Nottingham, UK, produces and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

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* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

YI contributed to the sections: how the intervention works, objectives, types of studies and participants, summary of findings table and subgroup analysis.

CC contributed to the sections: description of condition, types of interventions and selection of studies.

MW contributed to the sections: type of intervention, data extraction and management and outlined the outcome measures to be used.

HE contributed to the section: why is it important to do this review.

CM commented on the Methods section.

CK commented on the final protocol draft.

All review authors read and approved the final protocol version.

DECLARATIONS OF INTEREST

YI: none known.

CC: none known.

MW is an employee of Lancashire Care NHS Foundation Trust as a Substantive Consultant Psychiatrist. In addition, he has shares from Valirx and Eden Research Plc. All declarations are unrelated in any way that will prejudice this review.

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